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Letter to the Editor

Is pentraxin 3 a cardiovascular marker in patients with chronic Chagas disease?

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Chagas disease (CD) is a tropical neglected disease caused by *Trypanosoma cruzi*, which affects more than 8 million people in Latin America and represents an emerging problem in North America and Europe due to international migrations. Although most individuals infected by *T. cruzi* remain asymptomatic in the indeterminate form, after 10–20 years they may progress to one of the symptomatic forms of the disease, developing chronic chagasic cardiomyopathy (CCC), digestive megasyndromes, or both [1].

Cytokines and inflammatory mediators, including the complement system, are considered to contribute to the clinical progression of chronic CD. Even though the activation of complement system is essential to reduce parasite load during acute *T. cruzi* infection, it can cause tissue injury due to inflammation in CCC [2].

PTX3 is a multifunctional soluble pattern recognition molecule of innate immunity, which belongs to the long pentraxin family. Differently from C reactive protein, which is a short pentraxin produced in the liver. PTX3 is secreted at inflammatory sites by several cells, such as monocytes/macrophages and endothelial cells [3]. Thus, PTX3 has been considered a novel and probably more useful inflammatory marker for cardiovascular diseases.

Recent studies have demonstrated the involvement of PTX3 in different clinical disorders including cardiovascular diseases. While high PTX3 plasma levels were related to cardiac commitment in heart failure and associated with the risk to cardiovascular disease in metabolic syndrome, low plasma PTX3 concentrations were observed in patients with coronary artery disease and associated with metabolic syndrome and non-vascular injury resulted from previous myocardial infarction [4]. These studies reflect different roles for PTX3 in distinct inflammatory diseases and suggest that PTX3 may be a marker of clinical progression in heart diseases.

Considering the potential role for PTX3 as a risk factor for cardiovascular diseases and that no laboratory marker is available to indicate the progression from indeterminate to symptomatic CD, we aimed to determine PTX3 plasma levels in chronic CD patients (n = 128) from Southern Brazil using an ELISA commercial kit (Human Pentraxin 3/TSG-14, R&D®System, Minneapolis, USA). The cardiac patients were graded according to the cardiac insufficiency classification of the American Heart Association, adapted for Chagas disease (2005) [5] in A, B1, B2, C, and D groups. Demographical, laboratorial, and clinical findings of the specific CD forms are shown in Table 1. Moreover, 87 unrelated Southern Brazilians with negative *T. cruzi* serology and without clinical complaints were used as control subjects. All parameters were analyzed with adjustment for age, sex, and ancestry using logistic regression analysis. Formal written consent was obtained from each individual and the study was approved by the local medical ethics committee.

Plasma levels of PTX3 were significantly lower in CD patients when compared to controls ($p < 0.0001$, medians: 1.6 ng/ml and 2.7 ng/ml, respectively) (Fig. 1A). Although PTX3 levels were not related with cardiac commitment (cardiac A form versus B1 + B2 + C + D forms), different PTX3 levels were observed in the cardiac group when compared to indeterminate patients and controls ($p < 0.0001$). Moreover, a positive correlation between plasma PTX3 and Left Ventricular Ejection Fraction (LVEF) ($rho = 0.29$ and $p = 0.0048$) (Fig. 1B) was observed in the patients. There was a positive correlation between PTX3 levels and age in the controls ($rho = 0.37$, $p = 0.0027$), but not in patients and PTX3 levels were related with low HDL levels (<40 mg/dl) (1.72 ng/ml for low-HDL and 1.65 ng/ml for high-HDL, $p < 0.001$, OR 0.72, and CI 95%: 0.63–0.83) (Fig. 1C). In addition, PTX3 levels were also related to body mass index in patients (BMI) (rho = 0.22 and $p = 0.05$), with PTX3 levels being lower in non-obese (BMI < 30 kg/m^2) than obese (BMI ≥ 30 kg/m^2) CD patients (medians 1.42 ng/ml and 2.01 ng/ml, respectively, OR 1.67 CI 95%: 0.45–6.15 $p = 0.04$) (Fig. 1D).

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Table 1
Clinical, demographical, and laboratorial features of the patients with chronic Chagas disease.

Parameters		Chagas disease clinical form			
		Indeterminate N = 41	Cardiac N = 52	Digestive N = 19	Cardiodigestive N = 16
Age (years)	Mean (min–max)	53.2 [34–69]	56.5 [34–84]	59.2 [36–84]	58.9 [37–73]
Sex	Female	28	25	15	7
	Male	13	27	4	9
Body mass index (kg/m^2)	(N) mean [min–max]	(34) 26.7 [19.5–36.6]	(30) 26.3 [18–35.5]	(16) 25.1 [18.4–31.2]	(4) 24.4 [20.8–27.9]
Predominant ancestry	Euro–Brazilian	36	34	12	13
	Afro–Brazilian	5	14	6	3
	Amerindian	0	3	1	0
	Asian–Brazilian	0	1	0	0
Cardiac commitment	A	N.a.	14	N.a.	6
	B1	N.a.	11	N.a.	5
	B2	N.a.	2	N.a.	0
	C	N.a.	23	N.a.	5
	D	N.a.	2	N.a.	0
Left ventricular fraction ejection (%)	(N) mean [min–max]	(27) 69 [59–78]	(41) 53.5 [24–82]	N.a.	(12) 56.3 [23–75]
Glucose (mg/dl)	(N) mean [min–max]	(29) 102.9 [77–239]	(38) 105.5 [82–373]	(14) 109.4 [89–162]	(11) 100.2 [88–115]
Total cholesterol (mg/dl)	(N) mean [min–max]	(31) 207.1 [124–272]	(42) 205.4 [120–331]	(11) 208.2 [157–267]	(12) 188.2 [119–253]
LDL cholesterol (mg/dl)	(N) mean [min–max]	(31) 131 [59.2–200.4]	(42) 156.3 [85–283]	(11) 160.4 [117–228]	(12) 140.8 [69–183]
HDL cholesterol (mg/dl)	(N) mean [min–max]	(31) 53.5 [28–80]	(42) 49 [27–114]	(11) 47.8 [31–70]	(12) 47.3 [29–76]
Triglycerides (mg/dl)	(N) mean [min–max]	(31) 112.4 [46–229]	(42) 140.2 [50–584]	(11) 140.7 [65–283]	(12) 115.5 [60–179]
History of diabetes	(N)	3/35	3/49	2/18	1/16
History of hypertension	N.a.	22/35	23/49	10/18	6/16

Note: The functional classification of cardiac insufficiency according to Brazilian Consensus on Chagas disease (2005): **A**: altered electrocardiogram (ECG) and normal echocardiogram (ECHO), absence of cardiac insufficiency (CI); **B1**: altered ECG, LVEF >45%, absence of CI; **B2**: altered ECHO, LVEF <45%, absence of CI; **C**: altered ECG and ECHO, compensable CI; **D**: altered ECG and ECHO, refractory CI. Data is shown as numbers or mean [range]. N.a.: not applicable.

PTX3 is considered to have a dual function in the innate response, at one side protecting against unwanted complement activation, and on the other hand, enhancing complement-mediated tissue injury in situations such as ischemia or reperfusion [6].

PTX3 may mediate complement activation through the binding to different pattern recognition molecules including C1q, ficolins, and mannose-binding lectin (MBL) [6]. A pro-inflammatory role for MBL has been suggested in CCC and binding of both MBL and Ficolin-2 to *T. cruzi* was demonstrated in vitro [2]. On the other hand, PTX3 may interact with Factor H remaining functionally active, thus surface-bound PTX3/Factor H may prevent tissue damage associated with complement activation. Thus, low levels of PTX3 in patients with chronic CD may reflect an anti-inflammatory role for the protein, which might be in part related with Factor H interaction. Additionally, an anti-inflammatory

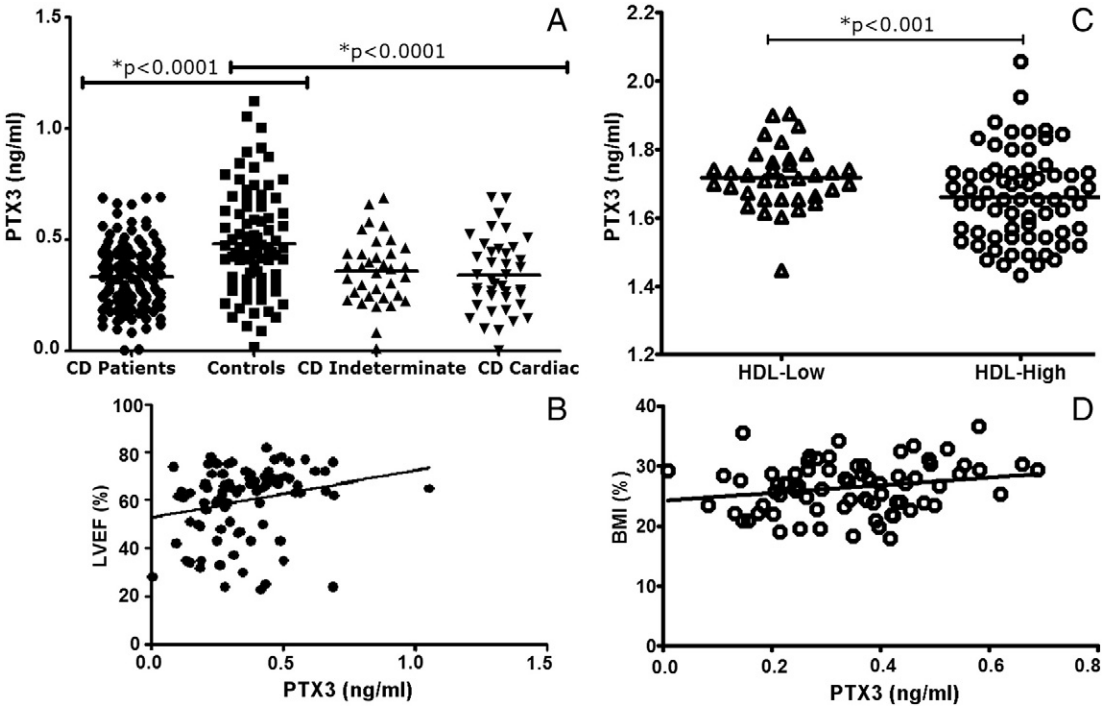

Fig. 1. Plasma PTX3 levels in patients with Chagas disease and its relation to risk factors for cardiovascular disease. **A.** PTX3 plasma levels in patients with Chagas disease and control subjects (*$p < 0.0001$, Kruskal–Wallis test); and in cardiac and indeterminate Chagas disease forms compared with control subjects (*$p < 0.0001$, Mann Whitney test). **B.** PTX3 plasma levels in high and low HDL patients ($p < 0.001$). **C.** Correlation between PTX3 plasma levels and left ventricular ejection fraction (LVEF) in patients with CD. **D.** Association between PTX3 plasma levels (ng/ml) and BMI (%): rho 0.22 and $p = 0.05$.

property for PTX3 has been reported in cardiac surgery and during clearance of late apoptotic cells by macrophages [7]. Moreover, exogenous administration of PTX3 was found to restrict the inflammatory response in experimental chronic granulomatous disease [8]. Low levels of PTX3 related to absence of disease activity were also found in systemic lupus erythematosus patients [9]. These studies corroborate with our findings indicating that PTX3 might play an anti-inflammatory property in chronic CD, conferring a cardioprotective role.

In contrast, high PTX3 concentrations were related to heart failure, contributing to cardiac commitment definition and associated with severity of dilative cardiomyopathy. Besides, increased PTX3 levels were observed in cardiac acute processes such as myocardial infarction and unstable angina [10]. Thus, these findings reflect different features of PTX3 in inflammatory process and suggest its use to assess clinical progression in cardiac disease.

Interestingly, we found a significant correlation of PTX3 with LVEF, which is an important cardiac function parameter. Although the pathophysiological role of PTX3 in the immune response is still unknown, this study suggests a protective role for PTX3 in chronic CD, being associated with cardioprotective function. Since low PTX3 concentration was also observed in CCC, it seems that low plasma PTX3 levels may be associated with cardiovascular risk factors in chronic CD.

In conclusion, our findings suggest an immunoregulatory role associated with cardioprotective feature for PTX3 in chronic CD. Further prospective studies should monitor plasma PTX3 levels in the follow-up of chronic patients with CD in order to confirm this effect of PTX3.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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